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**Allogeneic cardiospheres safely boost cardiac function and attenuate adverse remodeling after myocardial infarction in immunologically mismatched rat strains.**

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**Funding Grants:** Mechanism of heart regeneration by cardiosphere-derived cells

**Public Summary:**

We sought to characterize the immunologic profile of allogeneic cardiospheres, which are 3-dimensional, self-assembling, cardiac-derived microtissues, and to evaluate their safety and efficacy in repairing ischemic heart tissue.

**Scientific Abstract:**

**OBJECTIVES:** We sought to characterize the immunologic profile of allogeneic cardiospheres, which are 3-dimensional, self-assembling, cardiac-derived microtissues, and to evaluate their safety and efficacy in repairing ischemic heart tissue. **BACKGROUND:** Intramyocardial injection of autologous cardiospheres ameliorates remodeling and improves global function in infarcted myocardium. It is as yet unknown whether allogeneic cardiospheres are similarly effective without eliciting deleterious immune reactions. **METHODS:** We expanded cardiospheres from male Wistar Kyoto rat hearts and injected them surgically in the peri-infarct zone of Wistar Kyoto (syngeneic group, n = 28) and Brown Norway female rats (allogeneic group, n = 29). Female rats from both strains (n = 37) injected with normal saline served as controls. **RESULTS:** In vitro, cardiospheres expressed a low immunogenic profile and inhibited proliferation of alloreactive T cells. In vivo, cell engraftment was similar in the syngeneic and allogeneic groups 1 week and 3 weeks after transplantation. Reductions in scar size and scar collagen content and increases in viable mass in the risk region were accompanied by improvements in left ventricular function and attenuation of left ventricle remodeling that were sustained during 6 months of follow up. Transplantation of allogeneic cardiospheres increased tissue expression of the regenerative growth factors vascular endothelial growth factor, hepatocyte growth factor, and insulin-like growth factor-1, stimulating angiogenesis. Syngeneic and allogeneic cardiospheres attenuated the inflammatory response observed histologically in the peri-infarct region. **CONCLUSIONS:** Allogeneic cardiospheres increase viable myocardium, decrease scar, improve function, and attenuate adverse remodeling in the infarcted rat heart, without deleterious immunological sequelae. These observations lay the groundwork for developing cardiospheres as a novel off-the-shelf microtissue product for myocardial regeneration.

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